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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/079,929	02/19/2002	Sabina Sperandio	P-BU 5149	6504

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EXAMINER	
GAMETT, DANIEL C	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/079,929	SPERANDIO ET AL.	
	Examiner	Art Unit	
	Daniel C Gamett	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 28 October 2004.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-16 is/are pending in the application.

4a) Of the above claim(s) 1-3 and 7-10 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 4-6 and 11-16 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 7/24/2002.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

1. Applicant's election without traverse of claims 4-6 and 11-16 in the reply filed on 10/28/2004 is acknowledged. Claims 1-3 and 7-10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected claims, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/28/2004.

Claim Rejections-35 U.S.C. 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 4-6 and 11-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. Claims 4-6 are drawn to a method of inhibiting paraptotic cell death in a cell comprising contacting said cell with an effective amount of JNK inhibitor SP600125 wherein said effective amount of said compound inhibits paraptotic death of said cell (claim 4), wherein said paraptotic cell death is inhibited in a mammal (claim 5) or wherein said mammal is a human (claim 6). The specification provides no guidance as to how to inhibit paraptosis using SP600125. Indeed, the evidence that SP 600125 can inhibit paraptosis in any cells is indirect, being based on the observation "antisense oligonucleotide constructs for JNKI or JNK2 were able to inhibit

IGFIR-IC induced paraptosis in 293T cells" (on p.38, lines 9-14). These results are asserted, but no data are shown. Even with supporting data, these results would merely provide a basis for a hypothetical prediction that SP600125 is capable of inhibiting paraptosis in a model system. Further experimentation would be necessary to determine such critical parameters as dosage and timing for the use of SP600125 to inhibit paraptosis, if indeed it works at all. At the time of invention, the term "paraptosis" was newly coined; the cytological and biochemical differences between paraptosis and apoptosis were only beginning to be appreciated. The two forms of programmed cell death can be stimulated by the same stimuli (specification p. 6 lines 3-5: "Receptors involved in mediating cell death may activate either the paraptotic or apoptotic pathway, or may activate both pathways.") and can be inhibited by the same inhibitors (specification p. 6 lines 25-29: "inhibitors or neutralizing agents of the Jun N-terminal kinases (JNKs) ... block both the paraptotic and the apoptotic cell death pathways.") It was known that apoptosis may or may not require JNK activity in different situations, depending on the nature of the cell death signal (Sabapathy et al 1999, Curr Biol. 1999 Feb 11; 9(3):116-25) and it was not known whether paraptosis would be similarly variable. Under those circumstances, a skilled artisan can only tell by experimentation whether (a) paraptosis will occur and (b) SP600125 inhibits said paraptosis, in any particular system.

4. Claims 11-16 are drawn to methods of treating a condition associated with excessive cell death comprising administering to a subject in need of such treatment an effective amount of JNK inhibitor SP 600125 wherein said effective amount of said compound inhibits paraptotic death. Several conditions wherein programmed cell death is purported to be "non-apoptotic"

are contemplated (e.g. p.1, line 26-p.2 line 14; see also claims 13-16), but it remains unknown whether any of these instances of cell death represent paraptosis as defined by applicant and, most importantly, it remains unknown as to whether any of these processes are dependent upon JNK activity and so may be inhibited by SP600125. Even if a connection between said conditions, paraptosis, and JNK were established, that would teach only *why* to attempt to use SP 600125 for treatments, not *how* to use it. Thus, the specification offers no guidance as to critical matters that would enable treatments, such as patient selection, dosage, and the unpredictability that is inherent in extrapolating from a cell culture model to a complex system such as a diseased mammal. These unknowns will need to be addressed by extensive experimentation. Due to the large quantity of experimentation necessary to first establish the suitability of SP 600125 for inhibiting paraptosis and then to develop protocols for effective administration *in vivo*, the lack of direction/guidance presented in the specification regarding inhibition of paraptosis by SP 600125, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which established the unpredictability of a newly described program of cell death, and the breadth of the claims which fail to recite functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections-35 U.S.C. 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent,

> except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 4-6 and 11-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Bennett et al, US Patent Application 10395810, publication number 20040072888, 15 Apr., 2004, which claims benefit of US Provisional Patent Application number 60/24908, filed 19 Aug, 1999. These claims are drawn to a method of inhibiting paraptotic cell death (claim 4), particularly in mammals (claim 5) or humans (claim 6) and methods of treating a condition associated with excessive cell death, each method comprising contacting cells or administering to a subject an effective amount of JNK inhibitor SP600125 either alone (claim 10) or in combination with a known inhibitor of apoptotic cell death (claim 12). Claims 13-16 limit said condition from claim 11 to an ischemic condition, stroke, myocardial infarction, and neurodegenerative disease, respectively. Bennett et al. teach a method of contacting a cell in a mammal (as in claims 4 and 5) with an effective amount of the JNK inhibitor SP600125 (sections 0240-0247). SP600125 is a JNK inhibitor, and therefore it has the inherent property of inhibiting any cellular process that depends on JNK activity. If indeed paraptosis depends on JNK activity, in the absence of evidence to the contrary it must be assumed that inhibition of paraptosis occurs whenever SP600125 is administered to a cell or animal, especially if it can be shown that the administered dose was pharmacologically active. See also *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963) ("From the standpoint of patent law, a compound and all its properties are inseparable."). Therefore although Bennett et al. did not expressly state that the effect of SP600125 was to inhibit

paraptosis, such would necessarily result from administering SP600125 to mice treated with LPS (section 0241). Although Bennett *et al* did not state that human are the subjects, they do teach treatment of uniquely human disease such as Alzheimer's and thus Bennett et al anticipate claim 6. Bennett et al. also teach methods of treating conditions associated with excessive cell death (claims 11, 13-16; sections 0015 and 0016) with SP600125.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

8. A person shall be entitled to a patent unless –

    (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 4 and 5 are rejected under 35 U.S.C. 102(a) as being anticipated by Bennett *et al*, Proc. Nat. Acad. Sci. (USA) vol.98, no.24, Nov. 20, 2001. Claim 4 is drawn to a method of inhibiting paraptotic cell death in a cell comprising contacting said cell with an effective amount of JNK inhibitor SP600125 wherein said effective amount of said compound inhibits paraptotic death of said cell. Claim 5 limits the inhibition of paraptotic cell death recited in claim 4 to a mammal. Bennett *et al.* teach the use of SP600125 to inhibit the cell death that results from exposure of mouse T lymphocytes to anti-CD3 antibodies *in vivo*. Said cell death was referred to as "apoptosis" in the Bennett *et al.*, publication. Therefore, the only distinction between the instant claims and the prior art is recitation of "paraptosis" vs. "apoptosis". As noted above, SP600125 has the inherent property of inhibiting any cellular process that depends on JNK activity. SP600125 does not inhibit either paraptosis or apoptosis *per se*; it acts solely upon JNK. Inhibition of JNK remains the essential mechanism

of SP600125 regardless of the program of cell death that happens to be operating. Bennett *et al.* showed that SP600125 inhibits JNK and that it could be used to protect cells from programmed cell death. Even though paraptosis is a newly described program of cell death, the use of SP600125 to inhibit paraptosis does not constitute a novel use because its inhibitory mechanism is the same as that established by Bennett *et al.* Stated bluntly, the use of SP600125 to protect cells from programmed cell death was well known in the art at the time the instant application was filed and the subsequent showing that target for this inhibitor, i.e. JNK, is involved in a previously undiscovered death pathway does not make SP600125, nor any JNK inhibitor, a new invention.

Add 103 Statute

10. Claims 6 and 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bennett *et al*, Proc. Nat. Acad. Sci. (USA) vol.98, no.24, Nov. 20, 2001 as applied to claims 4 and 5, above, and in further view of Braun et al., Expert Opin Investig Drugs. 1999 Oct;8(10):1599-1610). Claims 6 and 11-16 are drawn to methods comprising use of SP600125 to inhibit paraptotic cell death in cells in a human (claim 6) or treating a condition associated with excessive cell death (claims 11-16). Said conditions are limited to a neurodegenerative condition in claim 16 or to ischemic conditions (claim 13), specifically stroke (claim 14) or myocardial infarction (claim 15). Bennett et al. do not specifically teach human use. However, it would have been obvious to one of skill in the art at the time the invention was made to extend the teachings of Bennett et al, to human cells and to treatment of the recited conditions with a reasonable expectation of success. The motivation to do so was noted by Bennett et al. on page 13686: "These findings support the hypothesis that JNK inhibitors may have clinical benefits in diseases involving cell death, including infarction, stroke, ischemia

reperfusion injury, and chronic neuronal cell death." Bennett *et al.*, do not teach combination therapy in which an inhibitor of paraptosis is used together with a compound known to inhibit apoptotic cell death as recited in claim 12. Braun et al., teach that apoptosis is most effectively inhibited when more than one branch of the apoptotic pathway are simultaneously inhibited. For example p. 1601, right column Braun et al., state: "inhibition of several caspases in the cascade often provides better protection than inhibition of a single caspase." Braun et al., explicitly suggest combination of caspase inhibitors with drugs that inhibit other aspects of apoptosis for the prevention of pathological apoptosis (p.1606, final paragraph.) It would have been obvious to one of skill in the art at the time the invention was made to use SP600125, as taught by Bennett et al., in a combination therapy as taught by Braun et al. with a reasonable expectation of success and with the motivation of achieving maximum protection from programmed cell death. The teachings of Braun et al. lend additional support to that already found in Bennett et al, for the use of SP600125 in human conditions as recited in claim 6, and 11-16.

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C Gamett,PhD, whose telephone number is 571 272 1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571 272 0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

DCG
Art Unit 1647
8 December 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER